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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/312,351	05/14/1999	JON A. WOLFF	MIRUS.006	2480

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EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/11/2001

13

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/312,351

Applicant(s)

WOLFF ET AL.

Examiner

Joseph Weitach

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 01 October 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 1-6 and 15-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7-14 and 18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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***Request for Continued Examination***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 1, 2001, paper number 12, has been entered.

**DETAILED ACTION**

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application filed May 14, 1999 claims benefit of provisional application 60/085,746, filed May 16, 1998.

Applicants' amendment filed October 1, 2001, paper number 11, has been received. The claim amendments have not been entered because they do not comply with 37 CFR 1.121 (see attached notice). Specifically, a separate unmarked copy of the newly amended claims should be present in the amendment, which will be entered as claim amendment. Appropriate correction in Applicants' next response is recommended. For the sake of compact prosecution, the proposed claim amendments for claims 7, 8, 12 and 18 will be examined in the instant action on the merits.

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Claims 1-18 are pending. Applicants' election of group III, claims 7-14 and 18, with traverse in paper number 5 is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). The requirement is still deemed proper and is therefore made FINAL.

Claims 1-18 are pending. Claims 1-6 and 15-17 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there as being no allowable generic or linking claim. Claims 7-14 and 18 are currently under examination.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-14 and 18 are rejected under 35 U.S.C. 112, second paragraph, for the reasons set forth in the Office Action of 9/20/00 and for the reasons set forth below as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 7 is unclear and confusing in the recitation of 'the compound having a disulfide bond' because the claim continues to list three separate conditions, (a)-(c), and the relationship of the conditions to this single disulfide bond is unclear. Does the compound have one disulfide bond which has or meets each of these conditions, or are there three disulfide bonds in the

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compound. In addition, if there is only one disulfide bond, it is unclear what free thiol group would be present for intramolecular attack in condition (c). Further, it is unclear from the general recitation of 'A compound' that a third thiol group is a limitation of said compound. Given the vague and broad nature of a compound and lack of any defining characteristics beyond having a disulfide group, any compound that meets the limitation of either (a), (b) or (c) would meet the limitation of and anticipate the claim. Dependent claims 8-11 are included in this rejection because they fail to clarify the basis of the rejection.

Given that the specification teaches that any type of molecule (i.e. protein, drugs, polynucleotides,...) can be linked to form a compound, and thus encompasses many different chemical substances, the claims as drawn to a 'compound' are being interpreted in the greatest reasonable breadth. Further, the breadth encompassed by the recitation of 'a compound' and the vagueness of any specific detail beyond the disulfide bond of the compound, the claim fails to clearly describe the metes and bounds of what is encompassed by the claim and will be interpreted in the breadth broadly encompassed by a compound as conventionally defined in the art.

Claims 10 and 11 are confusing because they are method claims which are dependent on claim 7 which is a product claim. In addition, there is no antecedent basis for the recitation of 'the polymer' in claim 10. Further, claim 10 is vague and unclear in the recitation 'the compound contains a ligand' because the nature of how a ligand is 'contained' in the compound is unclear. In light of the teachings in the specification, more clearly defining the nature of the compound in claim 7, or more clearly indicating the relationship of the components listed in

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claims 10 and 11 relative to the disulfide linkage comprised in the compound may obviate the basis of the rejection.

Claim 12 is unclear and confusing because it is a method for forming a compound, however the final step is to insert the compound into the organism. It is unclear if this final step is part of the process for forming the compound or if it is directed to the intended use recited in the preamble. If it is an active step for the generation of a compound, a final step wherein the compound is formed should be included.

Claim 18 is vague, unclear and confusing in the recitation of 'the compound is bi-functional' because there is a lack of antecedent basis for any function in claim 12. In light of the teachings in the specification 'bi-functional' appears to relate to the two ends of a linker molecule, however there is no teaching for any function for the compound. It appears that a linker molecule could link two separate functional proteins/molecules, however, the instant claims are not drawn to such a cross linked protein. It is unclear if the claim only intends to encompass the linker molecule or proteins/molecules cross linked with a linker which comprises a disulfide bond. Given the breadth encompassed by the recitation of 'a compound' and the vagueness of any specific detail beyond the disulfide bond of the compound, the claim fails to clearly describe the metes and bounds of what is encompassed by the claim and will be interpreted in the breadth broadly encompassed by a compound.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-14 and 18 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Applicants amendment to the claims have obviated the basis of the rejection. Specifically, the disclosure has ample literal and figurative support for linker molecules which contain cleavable disulfide groups, which upon reduction of the disulfide bond results in two molecules.

***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 7-14 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wagner *et al.* (Proc. Nat. Acad. Sci. USA 87(9):3410-3414, 5/1990), as evidenced by MacGillivray *et al.* (Proc. Nat. Acad. Sci. USA 79(8):2504-2508, 4/1982).

Applicants point out that the complex consisting of transferrin taught by Wagner *et al.* is N-acetylated. Applicants argue that the acetylated nitrogen found in transferrin and glutathione is less electron withdrawing than Applicants' nitrogen which in turn results in a lower pKa. In addition, by way of 37 CFR 1.132 declaration Applicants have also provided a chart illustrating the various pKa of compounds. See Applicants' arguments page 4. Applicants' arguments have been fully considered but not found persuasive.

First, it should be noted that the instant claims do not recite that the 'compound' encompassed by the claims contains any nitrogen. Examiner agrees that acetylation of a lysine would alter the chemical characteristics of the amino acid and in the context of a protein possibly the protein as a whole. However, in light of the breadth encompassed by the claim as discussed above in the 35 USC 112, second paragraph, rejections, the claims encompass a compound with a disulfide bond. In the instant case transferrin and the hetero-bifunctional crosslinker alone anticipate the claims. Further, as noted above, any compound meeting the limitation of one of the conditions set forth in (a)-(c) would anticipate the instant claims. The specification states that "cystine is reduced 3-15 times faster than oxidized glutathione" (p. 2, lines 30-31). Thus the intramolecular bonds in the compositions of Wagner meet the limitations of part (a) of claims 7 and 12; consequently, the rest of the arguments concerning acylation of cysteine amino groups and their resultant pKa values are not relevant.



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Claims 7-14 and 18 remain rejected under 35 U.S.C. 102(b) as being anticipated by Stassen *et al.* (Thrombosis and Haemostasis 74(2):646-654, 8/1995), as evidenced by Elliott *et al.* (J. Pharm. Exp. Therapeut. 273(1):280-284, 4/1995) and Voet (In Biochemistry, Second Edition, John Wiley and Sons, Publishers, 1995).

Applicants argue that for the reasons set forth in the rejection of Wagner *et al.*, claim amendments have obviated the anticipation of Stassen *et al.* See Applicants' arguments, page 4. Applicants' arguments have been fully considered but not found persuasive.

Applicants amendment does not obviate the rejection, since the claims are not limited to embodiments having "a disulfide bond that is activated by intramolecular attack from a free thiol thereby forming two molecules", but rather recites conditions wherein the compound has a disulfide bond that is cleaved more rapidly than oxidized glutathione or having a lower pKa than glutathione.

Claims 7-14 and 18 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) for the reasons of record and for the reasons set forth below as obvious over Wagner *et al.* (Proc. Nat. Acad. Sci. USA 87(9):3410-3414, 5/1990), as evidenced by Lodish *et al.* (J. Biol. Chem. 266(23):14835-14838, 8/1991).

Applicants argue that for the reasons set forth in the rejection of 35 USC 102 rejections, Applicants believe that the 102/103 rejection has been obviated. See Applicants' arguments, page 5. Applicants' arguments have been fully considered but not found persuasive.

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Applicants amendment does not obviate the rejection, since the claims are not limited to embodiments having "a disulfide bond that is activated by intramolecular attack from a free thiol thereby forming two molecules", but rather recites conditions wherein the compound has a disulfide bond that is cleaved more rapidly than oxidized glutathione or having a lower pKa than glutathione. Further, the conversion of the intermediate form of transferrin into a mature form requires breakage and establishment of disulfide bonds through the intramolecular attack by free cysteine.

*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached at (703)305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Kay Pinkney whose telephone number is (703)306-3553.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

*Deborah Crouch*  
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